16. (Amended) A method of detecting the relative proportions of PrP^{C} and PrP^{Sc} present in a composition, comprising:

mixing a composition that comprises prion proteins with a solution wherein [only [one form,] either PrP^{C} or PrP^{Sc}[,] is insoluble;

separating [the form of] soluble PrP [that is soluble from the form that is] from the insoluble PrP; and

determining the relative amounts of soluble and insoluble PrP.

19. (Amended) ~~The use of a~~ A protein stabilizing agent to improve a phenotypic defect in a cell that contains a conformationally defective target protein wherein the conformational defect causes the phenotype defect, wherein the protein stabilizing agent is selected from the group consisting of dimethylsulfoxide (DMSO), deuterated water, polyols; and amino acids and derivatives thereof, comprising contacting a first cell that expresses said conformationally defective target protein with an amount of a protein stabilizing agent that is effective to improve the conformational defect, thereby improving the phenotypic defect of the first cell in comparison with a second cell having the same conformationally defective target protein and phenotypic defect, wherein the second cell is not contacted with a protein stabilizing agent; wherein Congo Red is not the protein stabilizing agent.

REMARKS

A. The Invention

This application is a continuation in part of U.S. application no. 08/838,691, which issued as U.S. Patent No. 5,900,360. The present application was filed primarily to pursue claims withdrawn from consideration in the parent case pursuant to a restriction requirement (paper No. 5 dated 12/24/97 in U.S. application no. 08/838,691), and also to list additional chemical chaperones.

B. Status of the Pending Claims and Rejection

Claims 1-22 are currently pending.

The PTO has rejected dependent Claims 2-10, 12-15, and 17-18 under 35 U.S.C. § 112 (Second Paragraph) as indefinite for reciting "A" method. It rejected Claim 16, apparently for the recitation of "the form of Prp." The PTO also rejected Claims 11-15 under 35 U.S.C. § 112 (Second Paragraph) for allegedly omitting an essential element, a claim limitation describing assay parameters.

The PTO further rejected Claims 19-22 under 35 U.S.C. § 101 for the alleged recitation of a use without setting forth process steps.

Claims 1 and 5-8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-5 of U.S. Patent No. 5,900,360.

C. Response

1. Response to Rejections Under 35 U.S.C. § 112 (Second Paragraph)

The PTO rejected Claims 2-10, 12-15, and 17-18 under 35 U.S.C. § 112 (Second Paragraph) as indefinite for reciting "A" method. The claims are amended herein to recite "The method" instead of "A method." Applicants respectfully submit that the rejection is overcome by the amendment.

Claim 16 was rejected apparently for the recitation of "the form of Prp." Claim 16 has been amended to delete this term. Applicants respectfully submit that the rejection is overcome by the amendment.

Claims 11-15 were rejected under 35 U.S.C. § 112 (Second Paragraph) for allegedly omitting an essential element, a claim limitation describing assay parameters that are used to determine whether treatment with a protein stabilizing agent is "effective to improve the phenotypic defect." Applicants note that the specification teaches at pages 8-9 the following definitions for "phenotypic defect" and "improving a phenotypic defect:"

> "Phenotypic defect" denotes an observable and preferably readily quantifiable trait in a cell or organism, wherein the defect

is caused by a "conformationally defective target protein," that results in a medical condition or diseased state, as compared to wild type individuals whose protein is not conformationally defective.

"Improving a phenotypic defect" denotes causing a phenotypic defect in a cell or organism to observably or measurably become more like the wild type.

"Protein stabilizing agent" is a substance that stabilizes a protein in a biologically active conformation. For most proteins, it acts to stabilize the protein under conditions that can cause denaturation or aggregation. It stabilizes or induces a conformationally defective target protein to assume a biologically active conformation or compensates for its inability to assume a biologically active conformation, and causes a conformationally defective target protein to be processed properly, and/or to be targeted properly, and/or to acquire or retain a biological activity similar to that of the wild-type protein.

An amount of a "protein stabilizing agent" that is effective to improve a phenotypic defect is an amount that, when administered to a cell or individual having a conformationally defective target protein that results in a phenotypic defect, causes the phenotypic defect that is caused by conformationally defective target protein to become more like the phenotypic trait of cells or individuals that express the wild type protein. Protein stabilizing agents usually are administered at concentrations wherein a defective target protein is induced to behave like the wild-type protein, usually 1 μM to 1 M. The precise quantity may vary as a function of the relative potency of the protein stabilizing agent.

The application further states at page 12-14 physical property assays and biological activity assays for detecting correction of conformational and phenotypic defects. The application further describes assays for determining improvements in phenotypic defects with PrP (the parameter that is measured is solubility) and CFTR (the parameter is either subcellular fraction distribution, immunofluorescent localization, or forskolin dependent chloride efflux). Applicants respectfully submit that, based on the above information, a person of ordinary skill would understand that the parameter actually measured will vary depending on the identity of the conformationally defective protein and the nature of the resulting phenotypic defect.

Applicants respectfully submit that the current wording of Claim 12 defines the invention as precisely as possible. Any recitation of a particular parameter to be measured would claim less than what Applicants regard as their invention. Applicants further believe that, based on the teachings of the specification, a person of ordinary skill would readily be able to devise the appropriate parameters for defective proteins and phenotypic defects that are not specifically recited in the specification. Nonetheless, Applicants welcome suggestions by the Examiner that would meet his concerns without unduly limiting the scope of the claims.

2. Response to Rejection Under 35 U.S.C. § 101

Claims 19-22 were rejected under 35 U.S.C. § 101 for the alleged recitation of a use without setting forth process steps. Independent Claim 19 has been amended to recite process steps. Applicants respectfully submit that the rejection is overcome by the amendment.

3. Response To Rejection Under The Judicially Created Doctrine Of Obviousness-Type Double Patenting

Claims 1 and 5-8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-5 of U.S. Patent No. 5,900,360. Applicants note that Claims 1-8 of the present application are the same as Claims 1-8 of U.S. application no. 08/838,691, which issued as the '360 patent. In the parent application, Claims 1-8 were withdrawn pursuant to a 4 –way restriction requirement. See Restriction Requirement, paper No. 5 in the parent application. The issued Claims 1-5 of the '360 patent correspond to elected Claims 9-11 and 20-22.

Applicants understand that since the PTO has previously determined that the subject matter of Claims 1-8 of the parent application is separately patentable from the subject matter of Claims 1-8 of the parent and thus of the present application, it is improper to now reverse course and reject Claims 1 and 5-8 under the judicially created doctrine of obviousness-type double patenting. Applicants therefore respectfully request the withdrawal of the obviousness-type double patenting rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Hector A. Alicea
Reg. No. 40,891

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
HAA

SF 1080286 v1